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EXAMINER	
SHAFER, SHULAMITH H	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,183	ULMANN ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11,14,24-28,34,40,46,49-51,53,57,59,62,64-67 and 74-80* is/are pending in the application.

4a) Of the above claim(s) *1-3,11,14,24-28,34,40,46,49,51,53,57,59 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,64-67 and 74-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/7/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' response of 6 January 2011 is acknowledged. It is noted that there are no amendments to the claims in the instant application.

Claims 1-3, 11, 14, 24-28, 34, 40, 46, 49-51, 53, 57, 59, 62, 64-67 and 74-80 are pending in the instant invention. Claims 1-3, 11, 14, 24-28, 34, 40, 46, 49, 51, 53, 57, 59, and 62 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 50, 64-67 and 74-80 are under consideration.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 7 January 2011 has been considered. The signed copy is attached.

Withdrawn Objections

The objection to the specification as not in compliance with the requirements of 37 CFR 1.821 through 1.825 of the Sequence Rules and Regulations is withdrawn. Applicants have filed a computer readable form as required by section (e) and a statement that the “Sequence Listing” content of the paper or compact disc copy and the computer readable copy are the same thereby obviating the objection.

Maintained Rejections

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

The rejection of Claims 50, 64-67 and 74-80 under 35 U.S.C. 112, first paragraph, is maintained for reasons of record and for reasons set forth below. The specification, while being enabling for a method of inhibiting cell cycle of a cell *in vitro* comprising administering a Nup153 inhibitor to the cell, does not reasonably provide enablement for a method of inhibiting cell cycle of a cell *in vivo* comprising administering a Nup153 inhibitor to the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method of inhibiting a cell cycle comprising administering a Nup153 inhibitor to a cell wherein the Nup153 inhibitor is a peptide. The claims also recite a method of inhibiting a cell cycle comprising administering a Nup153 inhibitor wherein the inhibitor interferes with a Nup-153-COPI interaction. Given the broadest reasonable interpretation, the claims encompass administration of an inhibitor to an isolated cell, and to a subject comprising said cell (*in vivo* administration, as recited in claim 75). The claims are also broadly drawn to a method of treating cancer in a subject (as recited in claim 76).

The specification teaches a method of inhibiting a cell cycle of a cell comprising administering a Nup153 inhibitor to the cell in vitro [paragraph 0297 of PGPUB 20050226879, the PGPUB of the instant application]. The test system disclosed comprises cell free extracts derived from Xenopus eggs, which were used to form synthetic nuclei around sperm chromatin. When an inhibitor of Nup 153, a fragment

encompassing the central zinc finger domain of Nup 153, was included in the cell free system, inhibition of nuclear envelope breakdown was apparent [paragraph 0038]. Antibodies that specifically recognize Nup153 were able to prevent the normal progression of events in nuclear envelope disassembly. The nuclear membrane stayed largely intact after administration of said antibodies to the cell free extracts [paragraph 0161]. The disclosure teaches that methods which inhibit nuclear envelope breakdown may inhibit cancer cell proliferation [paragraph 0026]. Methods of identifying compounds that inhibit nuclear envelope breakdown are taught [paragraphs 0267-0272]. The disclosure contemplates utilization of the identified compounds to treat a subject with cancer [paragraphs 0302-0304].

Working examples: Examples 1 and 2 teach incubation of Nup153 fragments (Example 1) or synthetic peptides (13-meres) (Example 2) with cell free extracts derived from *Xenopus* eggs; these extracts form synthetic nuclei around sperm chromatin. Administration of these inhibitors of Nup 153 inhibits the breakdown of the nuclear envelope. There are no teachings, working or prophetic, of administration of inhibitors of Nup153 to cancer cells *in vitro* or administration of Nup 153 inhibitors *in vivo.*

Administration of a Nup153 inhibitor *in vivo* to inhibit cell cycle progression or to treat cancer is not enabled because the teachings in the specification provide insufficient guidance and objective evidence to predictably enable the use of the claimed methods *in vivo*.

In vitro assays, as detailed in the disclosure of the instant application are useful in determining basic physiological phenomena and in screening the effects of potential therapeutic compounds. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the controlled conditions of an *in vitro* assay does not permit a single extrapolation of in vitro assays to human treatment efficacy with any reasonable degree of predictability. It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Dermer (1994.

Bio/Technology 12:320) teaches that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. The reference teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. Dermer teaches that evidence of the contradictions between life in a Petri dish and in the body has been in the scientific literature for more than 30 years. "There have been major advances in the use of cell culture and recombinant human cells, and *in silico* approaches are also providing valuable alternatives to animal experiments by simulating drug interaction and response data. But, these studies still cannot predict the integrated response of a potential drug as accurately as living systems, in which a combination of genetic, biochemical, physiological, pathological and environmental influences work in concert" (Frantz. Nature Rev. Drug Dis. 2003. 2:501, 1st column, 3rd paragraph).

Additionally, the treatment of cancer in a subject is quite unpredictable as underscored by Gura (1997. Science 278:1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in vitro to in vivo protocols. The reference teaches that since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column), wherein the fundamental problem in drug discover for cancer is that the model systems are not predictive.

Furthermore, the nature of the invention is complex, involving the effects of proteins on biological systems. It is noted that the courts have long settled that such is considered complex. See Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), wherein it was determined that a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24

(CCPA 1970); Amqen Inc. v. Chuqai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Due to the large quantity of experimentation necessary to determine if administration of Nup153 inhibitors, wherein said inhibitors are peptides, *in vivo* would be effective in inhibiting cell cycle progression, and thus be effective in treating cancer in a subject, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of treatment of cancer in a subject and the breadth of the claims which fail to recite any limitations as to *in vitro*, undue experimentation would be required of the skilled artisan to practice the claimed invention in its full scope.

Applicants traverse the rejection (Response of 6 January 2011, page 6, 2nd paragraph, bridging page 15, 1st paragraph).

On page 8, 2nd and 3rd paragraphs, Applicants argue "At the time of the invention, it was known that cells undergo mitosis to reproduce and that the nuclear envelope dissolves in prophase. It was also known that cancer arises from a loss of normal cell growth control and that chemotherapeutic agents such as Taxol® and vinblastine, which interfere with steps in cell division, can be used to treat cancer. Techniques for making compounds such as proteins, peptides and nucleic acid based compounds were known in the art.

Using Xenopus egg extracts to study mitotic spindle assembly and function in vitro was a known and well accepted model system. See for example Methods in Cell Biology, Volume 61, 1998, Pages 385-412, Chapter 20 "The Use of Xenopus Egg Extracts to Study Mitotic Spindle Assembly and Function *in vitro*."

Applicant's arguments have been fully considered but have not been found to be persuasive.

The Examiner takes no issue with Applicants assertions that loss of normal cell growth control is known to be a contributing factor in cancer development. Nor is there any question that Taxol® and vinblastine, agents that effect spindle formation and cell

division are known to be effective cancer therapies. However, the fact that Taxol, which is not a peptide and does not target Nup153, is effective *in vivo* is not predictive that a peptide inhibitor of Nup153 would also be effective *in vivo*. The Examiner also acknowledges that the specification discloses a number of peptides that inhibit Nup153 activity *in vitro* and methods of producing such peptides.

However, applicants' claims are directed to a novel target for inhibition of cell cycle progression and cell proliferation and thus a novel therapeutic target for treatment of cancer. The specification has presented insufficient direction which would allow one of ordinary skill to predict that administration of peptide inhibitors of Nup153 could be directed to the appropriate target cell, cross the cell membrane and would be effective in inhibition of the cell cycle in vivo. Thus, the issue under discussion is whether one would be able to predict that peptides which inhibit cell cycle progression in an *in vitro* system, Xenopus egg extracts, would be effective in inhibiting cell cycle progression *in vivo* and would be effective in treatment of cancer in a subject. The reference cited, Desai et al. (Methods in Cell Biology, Volume 61, 1998, Pages 385-412, Chapter 20 "The Use of Xenopus Egg Extracts to Study Mitotic Spindle Assembly and Function *in vitro*.") details methods of preparing Xenopus egg extracts for spindle assembly, monitoring spindle assembly reactions, and manipulation of said extracts. The reference concludes "In this chapter we have described detailed procedures for the preparation of spindle assembly extracts, for manipulation of extracts to define the function of specific proteins in spindle assembly, and for the analysis of anaphase chromosome movement in vitro." The reference is silent as to whether results obtained in the Xenopus egg extract model would be predictive of results *in vivo*.

On page 9, 1st paragraph, applicants argue that the disclosed results predictably demonstrate that inhibiting breakdown of the nuclear envelope directly inhibits the cell cycle of a cell. Examples 1 and 2 of the present application present clear guidance on how to prepare inhibitors and test these inhibitors for the ability to inhibit the breakdown of the nuclear envelope and this inhibition of nuclear envelope breakdown is directly associated to the inhibition of the cell cycle.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The results disclosed in the specification of the instant invention present in vitro data indicating that peptide inhibitors of Nup153 inhibit breakdown of the nuclear envelope and said inhibition of nuclear envelope breakdown is associated with inhibition of the cell cytcle. However, Applicants have only taught methods of inhibiting a cell cycle in a cell by administering a Nup 153 inhibitor to a cell extract and to cell culture systems, that is, *in vitro*. The narrowly defined and controlled conditions of an *in vitro* assay system does not permit a single extrapolation of *in vitro* assays to human therapeutic efficacy with any reasonable degree of predictability. No model that can reasonably be correlated to the breadth of the claimed method has been presented.

On page 10, 1st paragraph, bridging page 11, last paragraph, Applicants argue:

Working Example 1 presents an in vitro model demonstrating that a fragment of Nup 153 encompassing the central zinc finger domain of Nup 153 provided a striking inhibition of nuclear envelope breakdown. Example 1 included studies using HeLa cells (a well-studied immortalized cervical cancer cell line) and cell-free extracts derived from Xenopus eggs to investigate the interrelation between COPI and Nup 153.

"Models using Xenopus egg extracts are recognized as correlating to a specific condition since studies using Xenopus egg extracts in vitro are widely used to study the cell cycle including cancer and potential treatment options. Applicants have provided two publications (Salisbury, et al., and Chang, et al.) to demonstrate the use of Xenopus systems to study cancer. These papers discuss studies using in vitro Xenopus egg assays in study of tissue sections from cancer patients (Microtubule Nucleating Capacity of Centrosomes In Tissue Sections) Salisbury, et al., (The Journal of Histochemistry & Cytochemistry, 1999 47(10) 1265-1273). Chang, et al., (Synthesis and Biological Evaluation of Myoseverin Derivatives: Microtubule Assembly Inhibitors (Journal of Medicinal Chemistry, 2001 44:26, 4497-4500)) discloses Xenopus egg assays used to screen compounds for inhibition of spindle assembly followed by testing against 60 cancer cell lines. Accordingly, Applicants submit that the in vitro studies

presented in the application using Xenopus egg extracts correlate with the claimed methods since over the years Xenopus model systems have become recognized as relevant to the study of the cell cycle including the cell cycle in human cancers. A recent review article also supports the use of Xenopus as a model system for studying cancer (Learning About Cancer From Frogs: Analysis Of Mitotic Spindles In Xenopus Egg Extracts (Cross MK, Powers MA, Dis Model Mech. 2009 Nov-Dec; 2(11-12):541-7). As stated in this paper "Much that has been learned from Xenopus extracts about cell cycle regulation, DNA replication and repair, and spindle assembly and function is proving to be relevant to human cancers." (see page 545).

In presenting the arguments that the in vitro results are not sufficient to support enablement the Examiner has cited Frantz. Frantz is directed to the decline of in vivo pharmacology studies; it is a general article on the need for more in vivo pharmacology studies and pharmacologists to do these studies. The Kamb and Roberts et al. publications cited by the Examiner are directed to problems with the predictive abilities of cancer models and clinical trials.

Applicant's arguments have been fully considered but have not been found to be persuasive.

As discussed above, Applicants have presented only studies comprising Xenopus egg extracts indicating inhibition of Nup153 activity inhibits nuclear envelope breakdown and cell cycling. The experiments with HeLa cells are not directed to inhibition of nuclear envelope breakdown. Rather, the data indicates a close juxtaposition of β-COP and nucleoporins [paragraph 03213].

The arguments of counsel cannot take the place of evidence in the record. Applicants assert "Models using Xenopus egg extracts are recognized as correlating to a specific condition since studies using Xenopus egg extracts in vitro are widely used to study the cell cycle including cancer and potential treatment options." However, the cited references make no such claims. Salisbury et al. is directed to an assay useful for identifying the position of the cell's major microtubule organizing center (MTOC) and its activity and for revealing differences in microtubule nucleation capacity between normal and diseased tissue and for cells at different cell cycle stages (page 1270, 2nd column,

last paragraph bridging page 1271, 1st column, 1st paragraph); one of the goals of the study was to show that centrosomes of tissue sections retain the ability to nucleate microtubules even after several years of storage as frozen tissue blocks (abstract). The Xenopus egg extracts were used in these experiments ***solely*** to support microtubule nucleation on tissue sections and touch preparations (page 1271, 2nd column). The reference is silent as to the applicability of results obtained by Xenopus egg extracts to potential treatment options. Chang et al. teach screening of myoseverin derivatives for inhibition of spindle assembly in Xenopus egg extracts. The reference notes that many compounds that bind to tubulin or microtubules and arrest the cell cycle by interfering with proper mitotic spindle assembly have high cytotoxicity, making them undesirable (page 4497, 1st column, last paragraph, bridging 2nd column, 1st paragraph), thus cautioning against extrapolating *in vitro* data to *in vivo* conditions. Cross et al, a post-filing date reference teaches that many spindle factors that have been found altered in cancer are conserved in Xenopus, and thus can be studied in the Xenopus system (page 545). However the reference cautions "Conclusions regarding the contribution of spindle checkpoint and spindle assembly factors to tumorigenesis are made difficult by the fact that many of these proteins have established or proposed alternate functions. Thus, definitive determination of which disrupted function is responsible for the observed increase in tumor formation is problematic." (page 546, 1st column, 2nd paragraph).

Thus, the preponderance of the evidence presented in the references cited by Applicants would lead one to conclude that data obtained in the Xenopus extract system is a good starting point in the development of therapeutic agents; but the art cautions on direct extrapolation to in vivo treatments.

With respect to the art cited by the Examiner:

Applicants question the relevance of the teachings of Frantz to the issue at hand asserting that Frantz is a general article on the need for more in vivo pharmacology studies and pharmacologists to do these studies. However, the cautions presented in the paper are relevant to the issues at hand. The reference emphasizes that in vitro studies "still cannot predict the integrated response of a potential drug as accurately as

living systems, in which a combination of genetic, biochemical, physiological, pathological and environmental influences work in concert." (page 501, 1st column, 3rd paragraph), thus cautioning against automatic extrapolation of in vitro results to the in vivo conditions.

The Kamb and Roberts et al. publications cited by the Examiner are directed to problems with the predictive abilities of cancer models and clinical trials. The Kamb paper emphasizes the difficulty of extrapolating results from cultured human tumor cell lines to the in vivo situation "One problem ….is the artificial nature of tumour cell lines that are typically passaged for many generahons in culture, and which might not be representalive of the tumor in its native state. Cells in culture lack the architectural and cellular complexity of real tumors, which incorporate inflammatory cells, vasculature and other stromal components (Kamb. Nature Rev. Drug Discovery. 2005:4:161-165, page 162, 2nd column, last paragraph). A direct measure of the low predictive value of preclinical screening for anti-cancer drugs is the low rate of response for Phase 1 clinical trials. Roberts, Jr et al., *JAMA* 292(17): 2130-2140 (2004), Table 4, shows response rates for the 1999-2002 period ranging from 0.4% to 5.3%; the overall response rate was 3.8%. Percentages this low clearly indicate that the pre-clinical screening as a whole is absolutely not predictive --- even a rate 10 times that high would indicate that the preclinical tests are not reliably predictive.

The art of record raises questions about the predictive values of tumor cell lines and other pre-clinical models. These cautions would certainly apply to the model system of the instant invention, Xenopus egg cell extracts.

At page 12 bridging page 13, 3rd paragraph, Applicants argue that considerable guidance and direction is provided on how to practice the invention. The nature of interference with the Nup 153-COPI interaction is described in detail, important structural regions of Nup 153 are identified: in particular the importance of the N terminal and C terminal regions surrounding the zinc finger regions and the zinc finger region itself is described. Applicants describe a fragment of Nup 153 encompassing the central zinc finger domain of Nup 153 in Example 1 which inhibited nuclear envelope

breakdown. The application provides extensive disclosure on how to make and use compounds of the present invention. In addition to the extensive guidance on how to make inhibitors, the specification provides extensive guidance on screening for the inhibitors of nuclear envelope breakdown. There is extensive guidance on the types of compounds that may be used as inhibitors, the regions of Nup 153 that could be targeted for inhibition and how to test these compounds for inhibitory activity. Given these teachings, one of ordinary skill in the art could, for example, refer to the guidance on the importance of the zinc finger structural region of Nup 153, make a peptide inhibitor of Nup153 based on this guidance and then test the inhibitor in an assay for Nup153 inhibition.

Applicant's arguments have been fully considered but have not been found to be persuasive.

There is no doubt that one can make peptides that may be potential inhibitors of Nup153 and screen such compounds in the Xenopus egg extract system. However, it is unpredictable that such peptides, administered to a subject with cancer, would act to inhibit nuclear envelope breakdown and inhibition of the cell cycle in said cancer cells in said subject.

At page 13, 4th paragraph, bridging page 14, applicants argue that there is a direct correlation between the demonstrated in vitro inhibition of nuclear envelope breakdown which is a fundamental requirement for the progression of the cell cycle and the in vivo of inhibition of the cell cycle. Based on the pharmacological activity of a Nup 153 inhibitor in inhibiting nuclear envelope breakdown a rigorous correlation, in particular in vivo data or clinical data is not required to satisfy the enablement requirement.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Applicants' claims are directed to a novel target for inhibition of cell cycle progression, and cell proliferation and thus a novel therapeutic target for treatment of

cancer. However, Applicants have only taught methods of inhibiting a cell cycle in a cell by administering a Nup 153 inhibitor to a cell extract and to cell culture systems, that is, *in vitro*. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The more that is known in the prior art about the nature of the invention, …..the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. (See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) (MPEP 2164.03).

With respect to predictability: If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. In the instant case, the nature of the invention is complex, involving the administration of proteins to biological systems. It is noted that the courts have long settled that such is considered complex. See Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), wherein it was determined that a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity.

The specification presents guidance as to the effects of inhibition of Nup153 in Xenopus egg extracts and the idea that such inhibition of Nup153 may be a useful therapeutic target for treatment of cancer in a subject. This constitutes an invitation to the skilled artisan to experiment to determine which embodiments might be functional. Such an invitation to experiment is not enabling.

The rejection is thus maintained.

Written Description

The rejection of Claims 50, 64-67, and 75-80 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record and for reasons set forth below. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Written Description Training Materials, Revision 1, March 25, 2008.

Claims 50, 64-67, 75, and 76 are directed to a method comprising administration a Nup153 inhibitor, wherein the Nup153 inhibitor is a peptide; claims 77-80 recite a method of inhibiting a cell cycle of a cell comprising administration of a Nup153 inhibitor.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

With respect to claims 50, 64-67, 75, 76 and 80:

A review of the language of the claim indicates that these claims are drawn to a method comprising administration of a genus, i.e., peptides which inhibit Nup153

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic

statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

The specification discloses the following information about a Nup153 inhibitor, wherein the inhibitor is a peptide:

A fragment encompassing the central zinc finger domain of Nup153 inhibits the breakdown of nuclear envelope when included in cell-free extracts derived from Xenopus eggs, which were used to form synthetic nuclei around sperm chromatin [paragraph 0038].

The inhibitory composition can bind a peptide, wherein the peptide comprises a sequence having at least 30%, 40%, 45%, 46%, 47%, 48%, 49%, 50%, 60%, 70%, 80%, 90%, or 100% identity to amino acids 658 to 891 of SEQ ID NO: 2 (the zinc finger domain of Nup153) [paragraph 0041]; however the structure of the binding peptide is not further disclosed nor is any relationship between the structure of the peptide and the ability to bind SEQ ID NO:2 described.

The inhibitors of nuclear envelope breakdown, such as inhibitors of Nup153-COPI interaction may have a relationship to the zinc finger region of Nup153. This region contains 5 zinc fingers connected by a variety of different linking regions. Thus, in certain embodiments two or more zinc fingers can be linked together to form an inhibitor. Molecules have this type can be represented by the formula I

$$-((Z_{..a}\text{-}L._{a}\text{-}Z._{b})\text{-}L._{b})_{n}$$

Wherein - $Z_{..a}$ and $Z._{b}$ represents a zinc finger

Wherein -$L._{a}$ and $L._{b}$ represents a linker which can be anything [paragraphs 0044-0050]

Inhibitory compositions that interact with the zinc finger region of Nup153, may be identified using any selection mechanism, such as phage display or a two-hybrid system. For example, CTTHPFTHECGGGS (SEQ ID NO: 30) was identified in a phage display experiment to a Nup153 zinc finger. This peptide in synthetic form as well as displayed form was capable of inhibiting nuclear envelope breakdown [paragraph 0053].

Antibodies that specifically recognize Nup153 were used in a nuclear disassembly assay. One antibody recognized the zinc finger region, and the other N-terminal region. Both antibodies were able to prevent the normal progression of events in disassembly [paragraph 0161 and Example 1].

Thus, the following species are within the scope of the claimed genus: fragments encompassing the central zinc finger domain of Nup153, the synthetic peptide of SEQ ID NO:30 and antibodies that specifically recognize Nup153. The disclosure of a few species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species (unspecified peptides) that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is peptides which inhibit Nup153. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

With respect to claims 77-79:

The claims recite administration of a Nup153 inhibitor, wherein the Nup153 inhibitor interferes with a Nup153-COPI interaction.

A review of the language of the claim indicates that these claims are drawn to a method comprising administration of a number of genera: compounds which interfere with Nup153-COPI interaction.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or

she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

To provide adequate written description and evidence of possession of a claimed genus or claimed genera, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant has identified the composition to be administered only by description of a function, the ability to interfere with Nup153-COPI interaction. However, the inhibitor is not further described by any common structural characteristics or structural/functional relationships.

In the instant application, the specification discloses a wide variety of compounds of different structural and functional characteristics which may exhibit the required functionality: inhibition of Nup153-COPI interaction. These compounds include, but are not limited to, a fragment encompassing the central zinc finger domain of Nup153 [paragraph 0038], variants of the Nup153 protein and derivatives of these proteins [paragraph 0140], chimeric proteins [paragraph 0191], antibodies to Nup153 [paragraph 0051, 0160], functional nucleic acids including antisense molecules, aptamers, ribozymes, triplex forming molecules, external guide sequences [paragraph 0087], RNA interference molecules (RNAi) or small interfering RNA (SiRNA) [paragraph 0092], small molecules [paragraph 0192], flavenoids [paragraph 0194] and synthetic peptides [paragraph 0359]. The specification teaches a single species of each of the following genera: variants of Nup153 (species: a fragment encompassing the central zinc finger domain of Nup153), antibodies (species: antibodies specific to Nup153), and synthetic

peptides (species: CTHPFTHECGGGS, SEQ ID NO: 30) as meeting the functional limitation stated in the claim.

Applicant has failed to provide any written description of most of the genera encompassed by the claim (variants of the Nup153 protein and derivatives of these proteins, chimeric proteins, and functional nucleic acids including antisense molecules, aptamers, ribozymes, triplex forming molecules, external guide sequences, RNA interference molecules (RNAi) or small interfering RNA (SiRNA), small molecules) and has only provided adequate description of a single species within each of three broad genera, as discussed above.

Claim 77 is thus a single means claim wherein the claim covers every conceivable structure (means) for achieving the stated purpose (inhibiting a cell cycle) but the specification at most discloses only three compositions.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera, which are inhibitors of inhibition of Nup153-COPI interactions. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genera. Therefore, only the following compounds: a fragment encompassing the central zinc finger domain of Nup153, antibodies specific to Nup153, and the synthetic peptide of SEQ ID NO:30 but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Applicants traverse the rejection (page 15, 2nd paragraph bridging page 19, 1st paragraph).

(a) On page 16, last paragraph, bridging page 17, 2nd paragraph) Applicants argue that a nucleic acid and protein sequence for Nup 153 is disclosed; important structural features of the protein. Given the identification of the zinc finger region, the Applicants provide possible constructs which include two or more zinc fingers. These possible constructs, along with the descriptive portions on calculating homology and

identifying acceptable amino acid substitutions and modifications are teachings as to the structure of Nup153 inhibitors.

(b) On page 17, last paragraph, bridging page 18, 4th paragraph, Applicants argue that working examples specifically demonstrating a fragment encompassing the central zinc finger domain of Nup153 which functions as an inhibitor have been provided, thereby illustrating the correlation between the zinc finger structure and the function of inhibition. Antibodies that specifically recognize Nup 153 were used in a nuclear disassembly assay (one antibody recognized the zinc finger region and the other the N terminal region) and both antibodies were able to prevent the normal progression of events in disassembly illustrating the functional importance of these regions in the function of Nup153. The peptide consisting of SEQ ID NO:30 was able to inhibit nuclear envelope breakdown.

(c) Applicants assert (page 18, last paragraph, bridging page 19, 1st paragraph), making the claimed invention are provided throughout the specification; thus one could readily make the inhibitors of the instant invention.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The MPEP states that if a biomolecule (for example, an inhibitor) is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure represents a sufficient number of representative species that encompass the genus: MPEP § 2163. ….Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of.species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

Applicants have disclosed three different types of inhibitors-the Nup 153 fragment, the antibody and the peptide; however, the claims encompass many more species and subspecies which are not further disclosed. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d916, 927,69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1). Adequate written description requires more than a mere statement that it is part of the invention and reference to potential method of making said peptide inhibitors or inhibitors that interfere with a Nup-153-COPI interaction.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The rejection is thus maintained.

Conclusion:

No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Primary Examiner, Art Unit 1647